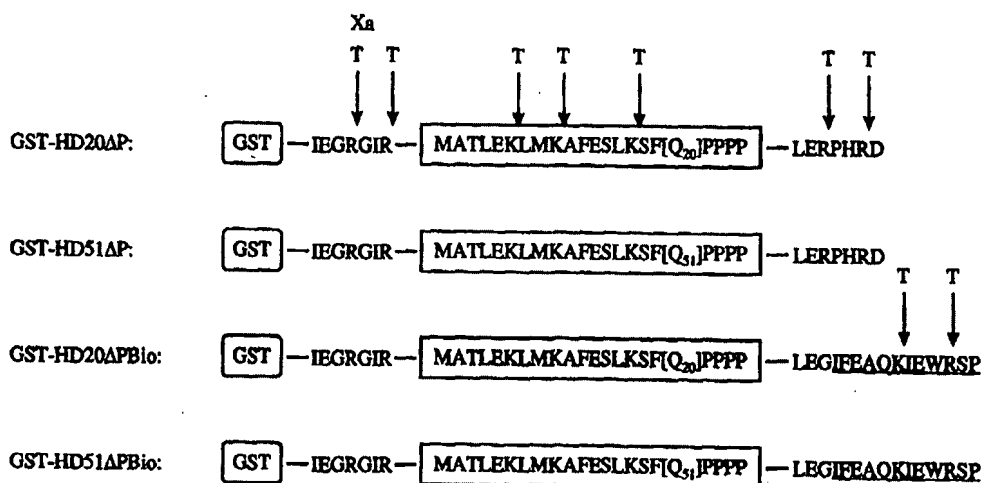




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | | |
|--|--|---|--|
| (51) International Patent Classification ⁶ : C07K 14/47, C12N 15/12, 15/62, C07K 16/18, C12N 15/63, A01K 67/027, A61K 48/00 | | A3 | (11) International Publication Number: WO 99/06545 |
| | | | (43) International Publication Date: 11 February 1999 (11.02.99) |
| (21) International Application Number: PCT/EP98/04811 | | (81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). | |
| (22) International Filing Date: 31 July 1998 (31.07.98) | | | |
| (30) Priority Data: 97 11 3306.1 1 August 1997 (01.08.97) EP | | Published With international search report. | |
| (71) Applicant (for all designated States except US): MAX-PLANCK-GESELLSCHAFT ZUR FÖRDERUNG DER WISSENSCHAFTEN E.V. [DE/DE]; Berlin (DE). | | (88) Date of publication of the international search report: 5 August 1999 (05.08.99) | |
| (72) Inventors; and (75) Inventors/Applicants (for US only): WANKER, Erich [AT/DE]; Leichhardtstrasse 61, D-14195 Berlin (DE). LEHRACH, Hans [AT/DE]; Lützelsteiner Weg 50, D-14195 Berlin (DE). SCHERZINGER, Eberhard [DE/DE]; Lützelsteiner Weg 52, D-14195 Berlin (DE). BATES, Gillian [GB/GB]; Division of Medical and Molec- ular Genetics, United Medical and Dental Schools, Guy's Hospital, Guy's Tower, 8th floor, London SE1 9RT (GB). | | | |
| (74) Agent: VOSSIUS & PARTNER; Postfach 86 07 67, D-81634 München (DE). | | | |

(54) Title: COMPOSITION AND METHOD FOR THE DETECTION OF DISEASES ASSOCIATED WITH AMYLOID-LIKE FIBRIL OR PROTEIN AGGREGATE FORMATION



(57) Abstract

The present invention relates to novel compositions useful for elucidating the onset or progress of diseases of preferably neuronal origin associated with the formation of amyloid-like fibrils or protein aggregates. Further, the present invention relates to methods for monitoring said formation as well as to methods for identifying inhibitors of said formation. Additionally, the invention relates to inhibitors identified by the method of the invention as well as to pharmaceutical compositions comprising said inhibitors.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|----|--------------------------|----|--|----|--|----|--------------------------|
| AL | Albania | ES | Spain | LS | Lesotho | SI | Slovenia |
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| AU | Australia | GA | Gabon | LV | Latvia | SZ | Swaziland |
| AZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | GH | Ghana | MG | Madagascar | TJ | Tajikistan |
| BE | Belgium | GN | Guinea | MK | The former Yugoslav Republic of Macedonia | TM | Turkmenistan |
| BF | Burkina Faso | GR | Greece | ML | Mali | TR | Turkey |
| BG | Bulgaria | HU | Hungary | MN | Mongolia | TT | Trinidad and Tobago |
| BJ | Benin | IE | Ireland | MR | Mauritania | UA | Ukraine |
| BR | Brazil | IL | Israel | MW | Malawi | UG | Uganda |
| BY | Belarus | IS | Iceland | MX | Mexico | US | United States of America |
| CA | Canada | IT | Italy | NE | Niger | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NL | Netherlands | VN | Viet Nam |
| CG | Congo | KE | Kenya | NO | Norway | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NZ | New Zealand | ZW | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's Republic of Korea | PL | Poland | | |
| CM | Cameroon | KR | Republic of Korea | PT | Portugal | | |
| CN | China | KZ | Kazakstan | RO | Romania | | |
| CU | Cuba | LC | Saint Lucia | RU | Russian Federation | | |
| CZ | Czech Republic | LI | Liechtenstein | SD | Sudan | | |
| DE | Germany | LK | Sri Lanka | SE | Sweden | | |
| DK | Denmark | LR | Liberia | SG | Singapore | | |
| EE | Estonia | | | | | | |

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/04811

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07K14/47 C12N15/12 C12N15/62 C07K16/18 C12N15/63
A01K67/027 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | WO 97 17445 A (CENTRE NAT RECH SCIENT ; INST NAT SANTE RECH MED) 15 May 1997 see page 3, line 7 - page 4, line 33 see page 14, line 10 - page 16, line 32; example 1 | 1, 13, 20 |
| X | C.A. GUTEKUNST ET AL., : "Identification and localization of huntingtin in brain and human lymphoblastoid cell lines with anti-fusion protein antibodies " PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, vol. 92, 1995, pages 8710-8714, XP002101176 cited in the application see page 8710 | 1-6, 8, 13 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

28 April 1999

Date of mailing of the international search report

21/05/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Mateo Rosell, A.M.

INTERNATIONAL SEARCH REPORT

Internat I Application No

PCT/EP 98/04811

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|---|-----------------------|
| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | <p>TROTTIER Y ET AL: "POLYGLUTAMINE EXPANSION AS A PATHOLOGICAL EPITOPE IN HUNTINGTON'S DISEASE AND FOUR DOMINANT CEREbellAR ATAXIAS" NATURE, vol. 378, no. 6555, 23 November 1995, pages 403-406, XP002009617 see the whole document and specially last paragraph</p> <p>---</p> | 1-6,13 |
| X | <p>M.F. PERUTZ: "Glutamine repeats and inherited neurodegenerative diseases: molecular aspects." CURRENT OPINION IN STRUCTURAL BIOLOGY, vol. 6, 1996, pages 848-858, XP002101177 cited in the application see the whole document but specially pages 853-856</p> <p>---</p> | 1-6,8,14,15 |
| X | <p>L. MANGIARINI ET AL., : "Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice" CELL, vol. 87, 1996, pages 493-506, XP002101178 cited in the application see the whole document</p> <p>---</p> | 2-6,23 |
| A | <p>WO 95 29243 A (UPJOHN CO) 2 November 1995 see page 7, line 18 - page 11, line 30</p> <p>---</p> | 1,8,15 |
| A | <p>EP 0 293 249 A (AMRAD CORP LTD) 30 November 1988 see abstract see page 2, column 2, line 40 - page 3, column 3, line 48 see page 8, column 13, line 36-51</p> <p>---</p> | 1,8,15 |
| A | <p>K. STOTT ET AL., : "Incorporation of glutamine repeats makes protein oligomerize: implications for neurodegenerative diseases" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, vol. 92, 1995, pages 6509-6513, XP002101179 cited in the application see the whole document</p> <p>---</p> <p style="text-align: center;">-/--</p> | 1,2,6,8 |

INTERNATIONAL SEARCH REPORT

Internat. Application No.

PCT/EP 98/04811

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|---|-------------------------------------|
| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | WO 96 28471 A (PHARM PEPTIDES INC) 19 September 1996 see abstract see page 3, line 5 - page 6, line 5 see page 7, line 10-26 see page 48, line 21 - page 53, line 15; examples 1,2 --- | 20-22 |
| X | MERLINI ET AL., : "Interaction of the anthracycline 4'-iodo-4'-deoxydoxorubicin with amyloid fibrils: inhibition of amyloidogenesis" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, vol. 92, 1995, pages 2959-2963, XP002101180 see the whole document --- | 20-22 |
| X | KISILEVSKI ET AL., : "Arresting amyloidosis in vivo using small-molecule anionic sulphonates or sulphates: implications for Alzheimer disease" NATURE MEDICINE, vol. 1, no. 2, 1995, pages 143-148, XP000611547 see the whole document --- | 20-22 |
| P,X | DATABASE WPI Week 9824 Derwent Publications Ltd., London, GB; AN 98-272215 XP002101183 & WO 98 18920 A (SRL INC.), 7 May 1998 see abstract --- | 1,2,5, 9-13 |
| P,X | US 5 723 301 A (STRITTMATTER WARREN J ET AL) 3 March 1998 see the whole document --- | 20-22 |
| P,X | E. SCHERZINGER ET AL., : "Huntingtin-encoded polyglutamine expansions from amyloid-like protein aggregates in vitro and in vivo" CELL, vol. 90, 8 August 1997, pages 549-558, XP002101181 cited in the application see the whole document --- | 1-6, 8-12, 15-18, 20,22,23 |
| | -/-- | |

INTERNATIONAL SEARCH REPORT

Internat' l Application No

PCT/EP 98/04811

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| P,X | <p>S.W. DAVIES ET AL., : "Formation of neuronal intranuclear inclusions underlies the neurological dysfunction in mice transgenic for the HD mutation " CELL, vol. 90, 8 August 1997, pages 537-548, XP002101182 cited in the application see page 539, discussion and page 546.</p> <p>-----</p> | <p>1-6,13, 23</p> |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/04811

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|----------------------------|---------------------|
| WO 9717445 | A | 15-05-1997 | FR 2741088 A | 16-05-1997 |
| WO 9529243 | A | 02-11-1995 | AU 2355895 A | 16-11-1995 |
| | | | EP 0758393 A | 19-02-1997 |
| | | | JP 9512426 T | 16-12-1997 |
| EP 0293249 | A | 30-11-1988 | AT 79902 T | 15-09-1992 |
| | | | AU 607511 B | 07-03-1991 |
| | | | AU 1793288 A | 21-12-1988 |
| | | | WO 8809372 A | 01-12-1988 |
| | | | CA 1338903 A | 11-02-1997 |
| | | | DE 3873989 A | 01-10-1992 |
| | | | DK 38189 A | 27-01-1989 |
| | | | ES 2045115 T | 16-01-1994 |
| | | | GR 3006173 T | 21-06-1993 |
| | | | JP 6081596 B | 19-10-1994 |
| | | | JP 1503441 T | 22-11-1989 |
| | | | NO 178894 B | 18-03-1996 |
| | | | US 5654176 A | 05-08-1997 |
| WO 9628471 | A | 19-09-1996 | US 5817626 A | 06-10-1998 |
| | | | US 5854215 A | 29-12-1998 |
| | | | AU 5252496 A | 02-10-1996 |
| | | | CA 2214247 A | 19-09-1996 |
| | | | EP 0815134 A | 07-01-1998 |
| | | | US 5854204 A | 29-12-1998 |
| US 5723301 | A | 03-03-1998 | NONE | |